PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SONN & PARTNER PATENTANWÄLTE
Riemergasse 14
A-1010 Vienna
AUTRICHE

- 5. Nov. 2004

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	02.11.2004

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
R 41446	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/07390	09.07.2003	12.07.2002

Applicant
AXON NEUROSCIENCE FORSCHUNGS-UND ENTWICK... et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Tikka, K Tel. +49 89 2399-7830

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
R 41446		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/07390	09.07.2003	12.07.2002
International Patent Classification (IPC) or both national classification and IPC		
C12N15/12		
Applicant		
AXON NEUROSCIENCE FORSCHUNGS-UND ENTWICK... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.01.2004	02.11.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Giebeler, K Telephone No. +49 89 2399-8546

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/07390

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-29 as originally filed

Sequence listings part of the description, Pages

1-9 as originally filed

Claims, Numbers

1-16 received on 14.10.2004 with letter of 14.10.2004

Drawings, Sheets

1/10-10/10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☒ contained in the international application in written form.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The documents of the state of the art are numbered D1 to D7 according to their respective position in the International Search Report.

2. NOVELTY

2.1. The subject-matter of claims 1-13 is considered to be novel over D1 to D4 since the term "which leads to the expression of an N- and C-terminally truncated tau molecule" in claim 1 is interpreted such that DNA constructs containing coding regions of full-length tau molecules, substitution mutants thereof, or truncated tau molecules of un-defined nature are not encompassed.

2.2. Claims 14-16 relating to a cell line and to an assay comprising it are considered to lack novelty over D5, see especially Examples 4 and 7. Consequently, the present application does not satisfy the criterion set forth in Article 33(1)(2) PCT.

3. INVENTIVE STEP

Concerning the issue of an inventive step, the Applicant has provided experimental evidence showing surprising features of the transgenic animal line #318.

Irrespective of the question of sufficiency of disclosure (see point 4 below), this specific transgenic animal cell line does indeed appear to show advantageous features which could not be derived from the available prior art in an obvious manner, and which could therefore establish an inventive step.

However, it is not credible from said experimental data that **all** transgenic animals according to claim 1 show this advantageous effect. This authority therefore considers that the claims cover subject-matter which does not involve an inventive step. Transgenic animals expressing deletion mutants of tau had already been

suggested at the present priority date (see for instance D2, page 2, lines 11-17). In the absence of a surprising, advantageous effect over the whole area claimed, no inventive step can be acknowledged for claims 1-16. It would have been obvious for a person skilled in the art to select truncated tau molecules as defined in the claims for expression as transgenes in order to solve the technical problem of merely providing further transgenic animals expressing truncated tau molecules.

4. It is pointed out that the application appears to severely lack sufficiency of disclosure (Article 5 PCT) and support by the description (Article PCT) since the description does not specify which truncated tau molecule and which promoter is used for expression in the transgenic animal "Tg line #318" referred to (page 22, paragraph 2). The information presented in Applicant's letter dated 14.10.04 as to which nucleotides were used for the transgene construction of transgenic animal line #318 cannot overcome this deficiency, since this information was not contained in the application as originally filed.

Claims:

1. A DNA construct which comprises a cDNA molecule coding for N- and C-terminally truncated tau molecules, wherein
- the molecules have truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence coding for 4-repeat and 3-repeat tau protein, respectively,as given in Seq.accession number NM_173727 in GeneBank
- the minimally truncated tau core encompasses a protein fragment which is encoded by nucleotides nr 744 - 930 (seq ID No. 9; numbered according to tau protein isoform 43)
- said DNA constructs are coding for proteins, which have neurofibrillary (NF) pathology producing activity when expressed in brain cells of animals.

2. A transgenic non-human animal of whose germ and/or somatic cells comprises the DNA construct according to claim 1.

3. Non-human animal whose germ and somatic cells transiently or stably express said DNA construct according to claim 1, thereby exhibiting NF pathology in the brain.

4. A transgenic non-human animal according to claim 2 or 3, preferably a rat, wherein the protein encoded by said DNA molecules is expressed in the brain.

5. Methods for genotyping of transgenic animals of any one of claims 2 to 4 using oligonucleotides specific for transgenic truncated tau according to claim 1.

6. A transgenic animal according to claim 4, developing NF pathology, and having a genetic background allowing the induction of risk factors associated with AD, thereby representing a disease model for humans.

7. A transgenic non-human animal of claim 6, which represents an animal model of AD, and permits induction of hypertension as a risk factor of AD.

8. A transgenic non-human animal of claim 6, which represents an animal model of AD, and permits induction of diabetes as a risk factor of AD

9. A transgenic non-human animal of claim 6, which represents an animal model of AD, and permits induction of hypercholesterolemia as a risk factor of AD.

10. A screening assay system and validation system for substances for the treatment, prevention and diagnosis of Alzheimer`s disease which comprises:

- evaluation of substances by:
  - detecting changes of neurofibrillar pathology in an animal according to any one of claims 2 to 4 and 6 to 9,
  - measuring of neurobehavioural changes in said animal,
  - measuring of the cognitive score in said animal,
- a validation system for substances for the treatment and prevention of tauopathies preferably AD,
- a validation system for the development of diagnostic markers and probes for the detection tauopathies preferably AD,
- a validation system for substances for the treatment of hypertension, diabetes, dislipidaemia and hypercholesterolemia in combination with tauopathies, preferably AD.

11. An experimental model system according to claim 10 for identifying new drug targets in tauopathies and related neurodegeneration processes preferably AD

12. Use of the animal according to any of claims 2 - 4 and 6 - 9 as an in-vivo assay to test the efficacy of substances, or therapies, in particular neurofibrillary pathology reducing therapies.

13. The use according to claim 12 wherein said substances or therapies are for neurodegenerative diseases, in particular tauopathies, preferably AD and other neurodegenerative diseases accompanied by neurofibrillary pathology.

14. A cell line transformed with a construct according to claim

1 or being derived from a transgenic animal of any one of claims 2 to 4 and 6 to 9.

15. A cell line according to claim 14, characterised in that the cell line is a rat cell line derived from a transgenic rat embryo.

16. An in vitro assay comprising a cell line according to claim 14 or 15, where said assay is employed as a screening and validation tool for the discovery of therapeutic preventive and diagnostic compounds and markers for Alzheimer's disease.